nucleotides themselves. McIlwain[9] has reported that pyridine 3-sulfonic acid inhibits the conversion of nicotinic acid to nicotinamide by *Staph. aureus*. Teply, Axelrod, and Elvehjem[10] found that nicotinamide, nicotinamide-ribose nucleoside and coenzyme I were of about equal potency in partially counteracting sulfapyridine bacteriostasis of *L. arabinosus*. Considerably larger amounts of nicotinic acid had no effect. The fact that both Teply *et al.*[10] and Dorfman and Koser[1] found larger amounts of coenzyme I to be necessary in the presence of sulfapyridine than under normal conditions does not necessarily invalidate the theory that the drug does not interfere with the function of the coenzyme I molecule. It is possible that coenzyme I is broken down before it is taken in by certain bacterial cells. It is also possible that in the respiration of intact cells, coenzyme I is continually broken down and sulfapyridine or sulfathiazole interferes with its resynthesis. This latter viewpoint is considerably strengthened by the work of Morel[11] who found that coenzyme I disappears from Proteus cells metabolizing pyruvate, and its content can be maintained if nicotinamide is supplied. She concludes that the coenzymes "wear out" while functioning only if there is an occasional irreversible change of the nicotinamide.

Summary. Our results indicate that sulfonamides do not interfere directly with the functioning of coenzyme I in yeast fermentation or in several systems in normal rat liver. The available experimental evidence does suggest the possibility that the drugs may inhibit the synthesis of the coenzymes.

9 McIlwain, H., *Brit. J. Exp. Path.*, 1940, **21**, 136.

10 Teply, L. J., Axelrod, A. E., and Elvehjem, C. A., *J. Pharm. and Exp. Therap.*, 1943, **77**, 207.

11 Morel, M., *Ann. inst. Pasteur*, 1941, **67**, 285.

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Structural Particularities of Antifibromatogenic Steroids: Experiments with Δ^4-androstene-3,17-dione and Cholestenone.*†

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The senior writer has called attention to the fact that the naturally occurring steroids which prevent abdominal fibroids induced by estrogens in the female guinea pig were all Δ^4-3-keto-steroids,[1] as progesterone, desoxycorticosterone, dehydrocorticosterone, and testosterone. There was apparently a parallelism between the progestational and antifibromatogenic activities of these substances; the antifibromatogenic activity of progesterone was greatly superior to that of testosterone propionate[7] or of Δ^{16}-dehydroprogesterone which was not antifibromatogenic.[3] The question arises how other Δ^4-3-keto-steroids known to have little or no progestational activity might behave when administered simultaneously with fibromatogenic quantities of estrogens. Two naturally not occurring

* This investigation has been aided by grants from the Jane Coffin Childs Memorial Fund for Medical Research, and the Rockefeller Foundation.

† This work has been done in collaboration with Dr. F. Giral, of the Instituto Politécnico and of "Laboratorios Hormona" in México City, who suggested the experiments with cholestenone. Thanks are due to Dr. F. Giral for this steroid and to Dr. Karl Miescher of Ciba Pharmaceutical Products in Basel for androstenedione.

1 Lipschütz, A., *Rev. Med. y Alim* (Chile), 1941, **4**, 329; *Revue Canad. de Biol.*, 1943, **2**, 92.

2 Lipschütz, A., Vera, O., and González, S., *Cancer Research*, 1942, **2**, 204.

3 Lipschütz, A., Bruzzone, S., and Fuenzalida, F., *Rev. Med. y Alim.* (Chile), in press.

TABLE I.
Comparative Fibrous Tumoral Reaction in Castrated Female Guinea Pigs with Subcutaneous Tablets of Alpha-estradiol and Different Δ^4-3-keto-steroids. Necropsy 90 to 95 Days after Implantation.

Estradiol absorbed per day, μg	Δ^4-3-keto steroid absorbed per day, μg	Avg fibrous tumoral effect F.T.E.*	No. of animals, total	No. of animals reaching avg F.T.E. of estradiol group	Avg No. of tumoral values 2 and 3 per animal	Uterine wt, g
16-57	0	5.7	23	12	1.9	4.9 (2.7-12.0)
	Androstenedione					
25-71	157-567‡	4.6	10	3	1.4	3.3 (2.0-5.7)
	Cholestenone					
12-17	60-158	5.2	6	3	1.8	3.8 (2.0-5.3)
	Progesterone					
21-63	13-24‡	1.4	14	0	0	3.0 (1.7-5.1)
	Testosterone†					
18-49	43-59‡	1.4	9	0	0.1	2.8 (1.0-5.5)

* The "fibrous tumoral effect" or F.T.E. represents the sum of 4 numerical values relating to the size of tumors of the uterus (subserous, mesometrial), "apical" tumors (or tumors of the mesosalpinx), tumors of the digestive tract and the abdominal wall, and splenic tumors. The tumors of each of these 4 regions are arranged in 4 classes characterized by the values 0.5, 1, 2, and 3, according to the size given in Fig. 1 in the paper of Lipschütz *et al.*[7]

† The *free* steroid has been used in these experiments. Fibroids occasionally occurred even when 200 μg of testosterone propionate per day were absorbed. See the diagram on page 86 in Lipschütz, A., *Cold Spring Harbor Symposia on Quant. Biol.*, 1942, **10**, 79.

‡ Non-selective absorption from tablets of the Δ^4-3-keto-steroid mixed with cholesterol.

Δ^4-3-keto-steroids were tried: androstenedione and cholestenone. According to older statements[4] Δ^4-androstenedione is even less progestational in the rabbit than free testosterone; according to new work the progestational activity of these two androgens coincides.[5] Cholestenone is seemingly void of any hormonal action in the body.[6]

Experiments were done in the manner customary in this Department: tablets of the steroids mentioned were implanted into castrated female guinea pigs simultaneously with estrogenic tablets which when alone present in the body induce, in the course of 3 months, abdominal fibroids in most animals, with an average fibrous tumoral effect of about 5 according to the classification explained previously.[7] Androstenedione (M.P. = 172°)‡ was mixed with 20% of cholesterol to give hard tablets; one to 2 tablets of 25 to 30 mg each were implanted subcutaneously. Absorption of androstenedione was not selective.‡ Cholestenone (M.P. = 78-80°) was used without any admixture; 3 to 4 tablets were implanted simultaneously. Necropsy was made 90 to 95 days after implantation of tablets. The results are given in Table I.

All animals receiving androstenedione had abdominal fibroids. The average F.T.E. was 4.6. It is remarkable that there were large abdominal fibroids even in those cases in which 400 μg of androstenedione per day or more were absorbed. The significance of this finding becomes evident when one remembers that about 13 to 24 μg of progesterone per day are sufficient to produce a very striking antifibromatogenic action (see Table I). Comparison with testosterone also is of interest. Though fibroids induced by estradiol

[4] Klein, M., and Parkes, A. S., *Proc. Roy. Soc., B*, 1937, **121**, 574.

[5] Selye, H., and Masson, G., *J. Pharm. and Exp. Therap.*, 1943, **77**, 301.

[6] Selye, H., *Endocrinology*, 1942, **30**, 437.

[7] Lipschütz, A., Bellolio, P., Chaume, J., and Vargas, L., PROC. SOC. EXP. BIOL. AND MED., 1941, **46**, 164.

‡ Determinations of M.P. and of the percentage of cholesterol at the end of the experiments were made by Dr. F. Fuenzalida of this Department.

may occasionally occur even when 200 μg of testosterone per day are absorbed[2] they do not usually occur with an absorption of only 40 μg per day (see Table I). The difference in results with Δ^4-androstenedione and testosterone were not due to differences in their masculinizing faculty. Though the capon unit of androstenedione is about 8 times that of testosterone[8] the quantities of androstenedione used in the present work were so considerable that the typical penis-like organ[9] was present in all animals. The corpus cavernosum reached in one case (with 500 μg per day) a length of 5 mm and the horny styles a length of 2 mm.

Sixty to 158 μg per day of cholestenone (M.P. = 78-80°) were absorbed. This is 10 times more than the antifibromatogenic threshold of progesterone. Abdominal fibroids were present in all 6 animals, and the average F.T.E. was not less than with estradiol alone.

As judged by the average F.T.E. androstenedione and cholestenone were not antifibromatogenic. Other criteria also supported this conclusion: the percentage of animals reaching the average F.T.E. of the estradiol group was slightly if at all influenced by androstenedione or cholestenone. The same is true concerning the average number of tumoral marks of classes 2 and 3 (tumors with a diameter of not less than 3 millimeters).

Uterine weight was smaller than with estradiol alone. Because of great variations we cannot say whether the difference is significant, but this may be an indication that with quantities still greater some antiestrogenic action might be obtained with the two substances.

Summary. Quantities of Δ^4-androstene-3-17-dione up to 40 times greater than the antifibromatogenic threshold of progesterone were not sufficient to prevent abdominal fibroids induced by alpha-estradiol. These quantities of androstenedione were also many times greater than the antifibromatogenic quantities of testosterone. The masculinizing action on the clitoris of the guinea pig was so pronounced as with testosterone. Quantities of cholestenone 10 times those of progesterone revealed no antifibromatogenic activity.

8 Goldberg, M. W., *Ergebn. d. Vitamin u. Hormonforsch.*, 1938, **1**, 37, 403, 405.

9 Lipschütz, A., *The Internal Secretions of the Sex Glands*, Cambridge (England), Baltimore, 1924, 301.

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Differential Behaviour of the Liver Towards Natural and Artificial Estrogens.*

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It has been known since the work of Biskind and associates that estrogens absorbed from intrasplenic pellets are inactivated in the liver.[1] The same has been stated concerning intrasplenic injections of estrogens.[2,3] These statements have been applied also to the study of abdominal fibroids induced by

* This work has been aided by the Jane Coffin Childs Memorial Fund for Medical Research, and the Rockefeller Foundation. Thanks are due to Prof. C. E. Dodds for hexestrol; to Messrs. Squibb and Sons, New York, and Instituto Sanitas, Santiago, for stilbestrol; to Dr. Karl Miescher in Basel and Dr. E. Oppenheimer of Messrs. Ciba Pharmaceutical Products in Summit for natural estrogens.

1 Biskind, G. R., and Mark, J., *Bull. Johns Hopkins Hosp.*, 1939, 212. Quoted from Biskind, G. R., and Meyer, M. A., *Endocrinol.*, 1941, **28**, 217.

2 Segaloff, A., and Nelson, W. O., PROC. SOC. EXP. BIOL. AND MED., 1941, **48**, 33.

3 Fels, E., *Medicina* (Buenos Aires), 1942, **2**.